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Research letters



Importance of both folic acid and vitamin B12 in reduction of risk of vascular disease

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Fortification of food with folic acid to prevent neural-tube defects in babies also lowers plasma total homocysteine, which is a risk factor for vascular disease. We investigated the effect of folate and vitamin B12 on homocysteine concentrations. 30 men and 23 women received sequential supplementation with increasing doses of folic acid. After supplementation, the usual dependency of homocysteine on folate diminished, and vitamin B12 became the main determinant of plasma homocysteine concentration. This finding suggests that a fortification policy based on folic acid and vitamin B12, rather than folic acid alone, is likely to be much more effective at lowering of homocysteine concentrations, with potential benefits for reduction of risk of vascular disease.

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Mandatory fortification of grain foods with folic acid has been in place in the USA since 1998, and evidence just published suggests that this measure has resulted in a 19% reduction in occurrence of neural-tube defects.¹ In the UK, mandatory folic-acid fortification is now a prospect after it was proposed by the Government's Committee on Medical Aspects of Food and Nutrition Policy (COMA). The COMA report² is currently undergoing consultation with the four UK Health Departments and the Food Standards Agency. If the report is approved, new legislature for compulsory fortification of wheat flour with folic acid will have to be drawn up. Although the COMA report focused mainly on the role of folic acid in prevention of neural-tube defects, the potential benefit of folic acid in reduction of risk of cardiovascular disease by lowering of concentration of homocysteine³ was also addressed, and undoubtedly contributed to the conclusions of the report.

As well as folate, remethylation of homocysteine to methionine requires vitamin B12, which has proved to be a far less effective determinant of plasma homocysteine concentrations than folate.⁴ We suggest that the reason for this conclusion is not because vitamin B12 has no important role in this process, but rather that the effect of vitamin B12 is often masked by the role of folate. We investigated the association between homocysteine and folate and vitamin B12 status in men and women, before and after supplementation with folic acid.

We used two interventions. 30 healthy men (age 34-65 years old) who had normal concentrations of folate and vitamin B12 had intervention one. 23 healthy women, selected by the same criteria as for intervention one, had intervention two. Participants did not consume food fortified with folic acid and did not take B-vitamin supplements before and during the study. No participants had a history of

vascular, hepatic, or renal disease or were known to have any haematological disorder or gastrointestinal disease. Ethics approval was granted by the Research Ethics Committee of the University of Ulster and patients gave written informed consent. We gave men folic acid at increasing doses, from 100 µg per day to 400 µg per day (table 1). Women received 500 µg per day folic acid. The total intervention period was 26 weeks, and participants were re-sampled at washout (10 weeks after completion of intervention).

	Serum folate (µg/L)*	Serum vitamin B12 (ng/L)	Homocysteine (µmol/L)
Intervention one (men, n=30)			
Preintervention	6.3 (5.0-10.0)	473 (396-547)	9.16 (7.8-10.3)
100 µg per day (weeks 0-6)	8.3 (6.6-11.2)	528 (378-658)	8.06 (7.3-9.1)
200 µg per day (weeks 7-12)	10.75 (8.7- 14.6)	505 (433-637)	7.38 (6.5-8.3)
400 µg per day (weeks 13-26)	17.65 (13.1- 20.3)	453 (405-569)	6.81 (6.4-7.8)
10 weeks post- intervention	8.4 (6.0-10.6)	510 (410-683)	8.18 (7.3-9.25)
Intervention two (women, n=23)			
Preintervention	8.6 (4.4-10.5)	616 (533-725)	11.00 (8.8-12.4)
500 µg per day for 4 months	15.5 (9.3-17.8) †	689 (500-720)	7.40 (5.6-7.9)†

*ANOVA p<0.0001. †Significantly different from preintervention, paired *t* test p<0.01.

Table 1: Median (IQR) concentrations of folate, vitamin B12, and total homocysteine concentrations in the two interventions

In intervention one, serum concentrations of folate rose significantly and of homocysteine fell significantly. Both compounds subsequently returned to baseline concentrations at washout (table 1). No change in serum vitamin B12 concentration was recorded over the intervention period in the participants. At baseline, a significant inverse relation was noted between plasma homocysteine and serum folate concentrations (table 2). This relation diminished in response to sequential doses of 100 µg per day, 200 µg per day, and 400 µg per day folic acid. Withdrawal of supplementation caused homocysteine concentrations to return to being dependent on folate. The converse effect was seen between homocysteine and vitamin B12 concentrations over the period of folic-acid supplementation. A weak relation existed between plasma homocysteine and serum vitamin B12 concentrations at baseline and in response to 100 µg per day folic acid. However, continued supplementation with 200 µg per day and 400 µg per day folic acid showed a significant inverse relation between plasma homocysteine and serum vitamin B12. This relation weakened 10 weeks after folic acid was withdrawn.

	Log serum folate			Log serum vitamin B12		
	<i>r</i>	Slope	<i>p</i>	<i>r</i>	Slope	<i>p</i>
Intervention one						
Baseline	-0.652	$y=-0.274x + 1.175$	0.0001	-0.261	$y=-0.212x + 1.513$	0.164
100 µg per day	-0.337	$y=-0.171x + 1.064$	0.065	-0.268	$y=-0.058x + 1.053$	0.122
200 µg per	-0.242	$y=-0.136x +$	0.065	-0.261	$y=-0.194x +$	0.050

day		1.009		1.395
400 µg per day	-0.080	$y=-0.014x + 0.086$ 0.868	-0.488	$y=-0.303x + 0.0016$ 1.661
Washout	-0.295	$y=-0.159x + 0.060$ 1.055	-0.310	$y=-0.141x + 0.0142$ 1.228

Intervention two

Baseline	-0.654	$y=-0.333x + 0.0001$ 1.30	-0.324	$y=-0.308x + 0.0019$ 1.873
500 µg per day	-0.334	$y=-0.187x + 0.0001$ 1.06	-0.472	$y=-0.441x + 0.007$ 2.08

r=correlation coefficient; y=log serum homocysteine; x=either log serum folate or log serum vitamin B12; p=probability of regression slope being significantly different from horizontal axis.

Table 2: Shift in circulating homocysteine dependency from folate to vitamin B12 with folic acid intervention

In intervention two, concentrations in serum of both folate and vitamin B12 were within the normal range (table 1). A strong inverse correlation between serum homocysteine and folate concentrations was shown in the pre-supplementation period, with a slightly weaker correlation between serum homocysteine and vitamin B12 concentrations (table 2). Conversely, after 4 months of supplementation with 500 µg per day folic acid, the relation weakened between serum homocysteine and folate concentrations, but strengthened between homocysteine and vitamin B12 concentrations.

Thus, whereas homocysteine concentration mainly depends on folate status, supplementation with folic acid above a certain concentration causes a shift in dependency from folate to vitamin B12, a dependency that reverts on withdrawal of folic acid. These results have important implications for the consultation process being undertaken by the UK Government on folic acid and prevention of disease.² If mandatory folic-acid fortification is introduced in the UK, the population would, in effect, be chronically supplemented with folic acid, allowing vitamin B12 to become the limiting nutrient for maintenance of normal homocysteine metabolism.

Our group has previously reported low vitamin B12 status to be a risk factor, independent of folate status, for neural-tube defects.⁵ We suggest that the probable reduction in risk of vascular disease by lowering homocysteine concentration will be more effective when a combination of folic acid and vitamin B12 is given, rather than folic acid alone. Taken together, findings of both this report and our earlier one⁵ suggest that greater benefits for disease prevention are likely to be achieved if vitamin B12 is included with folic acid in the new fortification programme under discussion.

Contributors

E Quinlivan had the original idea for the study and wrote the draft of the report. J McPartlin did homocysteine assays, supervised folate and vitamin B12 assays, did the statistical analysis, and wrote the report. H McNulty recruited patients, planned the study, and wrote the report. M Ward was responsible for recruitment of patients, study design, sample collection, and the intervention programme. J J Strain checked the study protocol was adhered to and wrote the draft of the report. D G Weir was responsible for the original intervention design and wrote the draft of the report. J Scott directed and supervised the study, wrote the draft of the report, and was responsible for samples.

Conflict of interest statement

None declared.

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